DNA encoding an immunogenic retroviral protein operably linked with a promoter and mannosylated polyethylenimine.

26. (New) The method of Claim 25, wherein the antiretroviral therapy further comprises a reverse transcriptase inhibitor selected from the group consisting of ddI, d4T, 3TC, AZT, FTC, delavirdine, abacavir, adefovir, nevirapine, efavirenz, tenofovir DF, adefovir dipivoxil, and mixtures thereof.

27. (New) The method of Claim 25, wherein the antiretroviral therapy further comprises a protease inhibitor is selected from the group consisting of, saquinavir, ritonavir, nelfinavir, atazanavir, and mixtures thereof.

Remarks

New Claims 22-27 are currently under consideration. The amended Claims find support at Claims 1-14 and 17-20, which have been cancelled without prejudice. Claims 15, 16 and 21 have been withdrawn, without prejudice, by the Examiner. Claims 24 and 26 find further support at page 23, line 3. Claims 23 and 27 find further support at page 23, line 8. The Claims and text have been amended to add generic drug names, atazanavir which has come into use for a material, BMS 232632, tenofovir DF for PMPA, and adefovir dipivoxil for PMEA, all of which were cited in the original specification. No new matter is added by any of these amendments. The text amendments are supported by the enclosed list of drugs from AidsMeds.com and drug information sheets.

Restriction Requirement

The Examiner had stated that Claims 1-14 and 17-20 were under consideration as they relate to administering antiretroviral drug therapy comprising ddI and indinavir until viral replication is effectively suppressed, and then administering a gene delivery complex as claimed, and that Claims 15, 16 and 21 are withdrawn from further consideration

pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicants respectfully point out that amended Claims are generic with respect to Claims 15, 16 and 21, as the latter group relates to an additional limitation that can be added to each of the above Claims. The applicant respectfully requests reinstatement Claims 15, 16 and 21 as claims depending from the current set.

Sequence Listing

The applicants again enclose hard and electronic copies of the sequence listings on page 34, lines 18 and 20. The enclosed sequence listings are identical to one another and to those on page 34. No new matter has been added. These sequences are not claimed.

Information Disclosure Statement

The same 6-page list of research articles discussed in the application as was enclosed with the previous response is again enclosed, together with hard copies of the articles, pursuant to the Examiner's request.

Objections to the Specification

The Examiner has objected to the Specification as follows:

The abstract is objected to as "not descriptive of the invention."

The first line of the specification needs updated to reflect the fact that 09/153,198 is now US Patent 6,420,176.

The status of US Patent Applications on pg 4, line 28, pg 11, line 23, pg 16, line 29, and pg 21, lines 5, 7 and 8, needs to be updated.

The description of the drawings has been objected to because the heading for Fig. 8 on pg 7, line 7, should be Fig. 8A-8C. The heading for Fig. 11 on pg 7, line 26, should be Fig. 11 A-1 1 B. The heading for Fig. 12 on pg 8, line 1, should be Fig. 12A1 2B. The heading for Fig. 13 on pg 8, line 4, should be Fig. 13A-13C.

Response

In response, the Specification has been amended as suggested by the Examiner. The status of US Patent Applications on pg 4, line 28, pg 11, line 23, pg 16, line 29 has been checked, and remain unchanged. The information on the other applications has been updated. The description of the drawings for Figs 7 and 9 has also been amended, for the sake of consistency.

Claim Objections - 35 USC § 112

1. Claims 1-14 and 17-20 have been objected to under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The Examiner states that administering an antiretroviral drug therapy comprising ddl and Indinavir until viral replication is effectively suppressed is considered enabled because Finzi taught administering a reverse transcriptase inhibitor and a protease inhibitor suppressed viral replication (Finzi et al. Science. Nov. 14, 1997, Vol. 278, pg 12951300). Claims 1-14 and 17-20 are not enabled because the structure of the gene delivery complex that is a "therapeutic genetic immunization" as claimed has not been adequately taught in the specification.

According to the Examiner, the state of the art at the time of filing was that the combination of vector, promoter, route of administration, level of expression and target tissue required to obtain a therapeutic or prophylactic effect using gene therapy was unpredictable. Miller of record (1995, FASEB J., Vol. 9, pages 190-199) is said to review the types of vectors then available for in vivo gene therapy, and conclude that "for the

long-term success as well as the widespread applicability of human gene therapy, there will have to be advances ... targeting strategies outlined in this review, which are currently only at the experimental level, will have to be translated into components of safe and highly efficient delivery systems" (page 198, column 1). Deonarain of record (1998, Expert Opin. Ther. Pat., Vol. 8, pages 53-69) is said to indicate that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Deonarain is said to review new techniques under experimentation in the art that show promise but state that such techniques are even less efficient than viral gene delivery (see page 65, first paragraph under Conclusion section). Verma of record (Sept. 1997, Nature, Vol. 389, pages 239-242) is said to review vectors known in the art for use in gene therapy and discuss problems associated with each type of vector. The teachings of Verma are said to indicate a resolution to vector targeting has not been achieved in the art (see entire article). Verma is also said to teach that appropriate regulatory elements may improve expression, but it is unpredictable what tissues such regulatory elements target (page 240, sentence bridging columns 2 and 3). Crystal of record (1995, Science, Vol. 270, page 404-410) is said to review various vectors known in the art and indicate that "among the design hurdles for all vectors are the need to increase the efficiency of gene transfer, to increase target specificity and to enable the transferred gene to be regulated" (page 409).

The Examiner says that the state of the art regarding treating retroviral infection was unpredictable. Stricker of record (Medical Hypotheses, June 1997, Vol. 48, pages 527-9) is said to teach that attempts to develop a vaccine against HIV have been unsuccessful because HIV vaccines do not neutralize HIV (pg 527, last paragraph through all of pg 528). The Examiner concludes that, overall, a lack of understanding about protective immunity to HIV in humans, the sequence variability of HIV and the rapid replication of HIV contribute the ineffectiveness of vaccines against HIV (Bangham of record, Nov. 29, 1997, Lancet, Vol. 350, pages 1617-1621 - page 1617, top of col. 1).

The Examiner notes that the present specification teaches a complex comprising i) manosylated PEI and ii) DNA encoding an immunogenic HIV protein operably linked to a promoter, and also that administration of the complex to a host after drug therapy was followed by an increase in CD4 cells then a decrease in CD4 cells (pg 53).

The Examiner states that the specification does not provide adequate guidance for one of skill to use a gene delivery complex comprising "foreign genetic material" as a "therapeutic genetic immunization" as claimed. The Examiner says that the results described in the specification are not considered therapeutic because the overall result does not result in a net increase in CD4 cells; that it cannot be concluded that the gene complex caused the initial increase in CD4 cells because the experiment did not include controls, that is, animals that did not receive drug therapy or the gene complex. The Examiner also states that the specification does not provide adequate guidance indicating the increase in CD4 was caused by the gene complex - the drug therapy could have caused the increase in CD4. The Examiner says that the specification did not teach treating animals that were already infected or challenging the animals after they were given DermaVir. The Examiner continues that, for administration of foreign genetic material to be a "therapeutic genetic immunization", the specification must overcome the unpredictability in the art by adequately describing the structure of the "foreign genetic material" used, the dosage and route of administration that results in a therapeutic effect or "immunization." The Examiner concludes that, without such guidance it would require one of skill in the art undue experimentation to overcome the unpredictability in the art regarding gene therapy and retroviral therapy to determine the combination of elements required to obtain a therapeutic or prophylactic effect against retroviral infection using "foreign genetic material, and so, the specification does not enable "therapeutic genetic immunization" using a gene delivery complex comprising "foreign genetic material" as claimed.

Response

In response, the Claims have been amended as suggested by the Examiner.

Claim Objections 1-14 and 17-20 under 35 USC § 112

2. Claims 1-14 and 17-20 are said to be not enabled because the specification allegedly does not provide adequate guidance to determine any complex that has a "specific affinity for a receptor of an antigen presenting cell" as claimed.

The Examiner states that the specification does not define "affinity" and does not teach any sugar, PEI, PEI derivative or mixture thereof that has a "specific affinity for a receptor on an antigen presenting cell." The Examiner states that the art at the time of filing did not teach sugars, PEI, PEI derivatives or mixtures thereof that had a "specific affinity for a receptor on an antigen presenting cell." The Examiner states that, for example, the specification contemplates using the mannose receptor for entry into dendritic cells; however, the mannose receptor is also found on macrophages (Stahl, Feb. 1998, Curr. Opin. Immunol., Vol. 10, pages 50-55; page 51, col. 2). The Examiner says the specification also contemplates using mannosylated-PEI which binds to the mannose receptor; however, the PEI component of mannosylated-PE1 may be internalized via the asialoglycoprotein receptor which is found on non-APCs (e.g. hepatocytes) (page 16, last sentence). The Examiner says the specification does not teach that mannosylated-PE1 is specific to the mannose receptor on APCs and that the PEI component could not be used to bind the asialoglycoprotein receptor on a non-APC (e.g. hepatocyte). The Examiner states that it would have required one of skill in the art undue experimentation to determine agents that specifically bound to receptors on antigen presenting cells and not to other receptors, and says that, therefore, agents having a "specific affinity" for receptors on antigen presenting cells are not enabled. The Examiner states that the specification does not enable suppressing any viral replication using any antiretroviral drug therapy" (claim 1) other than retroviral replication, because the specification and the art do not teach suppressing replication of any virus using antiretroviral drug therapy other than retroviral replication. The Examiner states that, in fact, many of the antiretroviral drug therapies describe in the specification inhibit reverse transcriptase, which is specific to retroviruses, and that, in particular, the combination of inhibiting

reverse transcriptase and protease is specific to retroviruses. The Examiner concludes that it would require one of skill undue experimentation to determine how to suppress replication of any virus using antiretroviral drug therapy other than retroviruses.

Response

In response, the Claims have been amended as suggested by the Examiner.

Objection to Claims 1-14 and 17-20 under 35 U.S.C. 112, second paragraph,

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention. Claims 1-14 and 17-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1. Claim 1 is said to be indefinite because the antiretroviral drug therapy and gene delivery complex are not administered to a host that is infected with a retrovirus. The Examiner comments that the claim should clearly set forth that the drug therapy and gene delivery complex are administered to something.

2. Claim 1 is said to be indefinite because antiretroviral drug therapy does not suppress any "viral replication" as claimed. The Examiner adds that, to be commensurate in scope, the antiretroviral drug therapy should suppress retroviral replication.

3. The term "effectively" in claim 1 is said to be indefinite. This commonly used claim term is said to be relative and therefore said to have no definition in the art or the specification. As such the metes and bounds of when replication is "effectively" suppressed cannot be determined.

4. The Examiner says the term "foreign" in claim 1-6 does not make sense. The term is said to be relative. The claim does not clearly set forth to what the genetic material is foreign, especially in view of the fact that the genetic material is not administered to a host of any kind.

The Examiner takes the position that it cannot be determined how "foreign genetic material" relates to the "nonviral vector" (claim 1), stating that it cannot be determined if the two components are mutually exclusive or if the components share overlap, and if the components share overlap, it cannot be determined how the components overlap.

5. The term "specific affinity" is said to be indefinite (claim 1, 11) allegedly because it cannot be determined if "specific" in context means the complex only has affinity for a receptor on an antigen presenting cell or if the complex has a preference for a receptor on an antigen presenting cell. Therefore, the metes and bounds of the complex cannot be determined.

The Examiner says the metes and bounds of "gene delivery complex" that have an affinity for a receptor on an antigen-presenting cell cannot be determined (claim 1), adding that it is unclear if the complex must bind to a receptor or if the complex merely has a chemical attraction to the receptor.

6. The metes and bounds of "reverse-transcriptase dependent virus" in claim 3 is said to be indefinite. The Examiner takes the position that it cannot be determined if the virus must have reverse transcriptase to exist if the virus must have reverse transcriptase to replicate, or if the virus must have reverse transcriptase to infect cells, and concludes that the metes and bounds of what applicants consider "dependent" cannot be determined.

7. The Examiner says the metes and bounds of what applicants consider a "substantial portion" of a replication defective HIV (claim 4-6) cannot be determined. How substantial is a "substantial portion?"

The Examiner takes the position that the metes and bounds of what applicants consider "an integrase negative mutant of a dual-tropic primary isolate of a human immunodeficiency virus" cannot be determined (claim 6), because it is unclear if the virus does not encode an integrase or if the virus is merely deficient at producing functional integrase. The Examiner says it is unclear how a virus is "dual-tropic" because the term does not have a definition in the art or the specification. The Examiner concludes that the

metes and bounds of a primary isolate of HIV are unclear because it cannot be determined if the term "primary" is limited to a virus isolated directly from a patient or whether the term encompasses a virus isolated directly from a patient and maintained over a period of time.

8. The phrase "the reading frames of the integrase gene" in claim 7 is said to lack antecedent basis in claim 6, and that the phrase also does not make sense because claim 6 requires the virus is "integrase negative." The Examiner comments that an "integrase negative" virus does not have reading frames of an integrase gene.

9. Claim 8 is said to be unclear, because the foreign genetic material or the non-viral vector may be DNA, but the complex is not DNA. The Examiner comments that it is unclear if the complex of claim 1 further comprises "one or more agents ... ... sugars, polyethylenimine... " or if the "one or more agents" is limiting one of the terms in claim 1.

The phrase "complex is DNA and one or more agents" (claim 8) is said to be grammatically incorrect. The Examiner takes the position that it is grammatically incorrect to describe a composition of one item (singular) by the use of one (singular) item in combination with multiple items of a single class agents (plural). The Examiner adds that, upon correcting the error, the species in the Markush group may also require correcting.

Claim 8 is said to be indefinite because the Markush Group is said to be improper. The Examiner states that sugars, PEI, and PEI derivatives are not species that share a genus, because the structure of sugars is materially distinct and separate than that of PEI or PEI derivatives. As such, the group is deemed improper.

10. Claim 9 is said to be indefinite because "sugar-modified polyethylenimine" does not clearly set forth the structure of the agent. The Examiner comments that it is unclear how the PEI is modified with sugar - is the sugar attached or merely used to alter the structure of PEI without attaching, and that it is unclear whether the "sugar-modified polyethylenimine" further limits the PEI or the PEI derivative in claim 8.

11. Claim 10 is said to be indefinite because it is unclear if glucose is further limiting the "sugars" or the "derivatives" of PEI in claim 8, and that the phrase "anti retroviral drug combination" in claim 17 lacks antecedent basis.

12. The Examiner takes the position that the metes and bounds of what applicants consider "highly active" antiretroviral drug therapy cannot be determined (claim 17) because it is unclear if the phrase refers to a particular combination of drugs or any drug or drug combination that has a particular activity. The Examiner comments that, if the phrase refers to drug or drugs that have a particular activity, the level of activity for a treatment to be considered "active" cannot be determined. While the Examiner admits the phrase was known in the art, he states that the phrase does not have a definition in the art or the specification. Therefore, the metes and bounds of such therapies cannot be determined.

13. The Examiner says that, to be in proper Markush format, claims 18 and 20 should have the phrase "selected from the group consisting of."

Response to Objections 1-13

In response, the applicants have amended the Claims as suggested by the Examiner.

Claim Objections 1-14 and 17-20 under 35 USC § 112 (cont'd)

14. Claims 19 and 20 are said to contain the trademark/trade name delavirdine, abacavir, adefovir, nevirapine, efavirenz, lubocavir, PMPA, PMEA, indinavir, saquinavir, ritonavir, nelfinavir, and GW41. Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. See Ex parte Simpson, 218 USPQ 1020 (Bd. App. 1982). The claim scope is said to be uncertain because the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the trademark/trade

name is used to identify/describe reverse transcriptase inhibitors and protease inhibitors and, accordingly, the identification/description is indefinite. In claim 19, a comma is required between PMPA and PMEA.

Response

The amended Claims use generic or established names for drugs, not trademark/tradenames. Due to their length and complexity, the chemical names of the referenced compounds are not well-known, and are not used for searching the literature. As a result, Congress has required that, if a prescription drug has an established name, it must be displayed with the trade name or trade mark on the label. (Sec. 502(e) of the Food and Drug Act and 21 CFR 202.1) and cross-references between the trade names and established are readily available (copies enclosed). The better policy on the part of the USPTO (and the general rule) is to use the established name for the drug in the claims, when this will facilitate searching. The applicants have amended the claims where a different name has become established for a new drug, and the text of the application has been amended in parallel, as well as to update source information. The enclosed web pages support the amendments. None of these amendments add new matter to the specification.

The applicants are willing, if the Examiner so requires, to insert the chemical names for each of these materials into the Claims along with the established names, but they respectfully submit that this will make the claims more, rather than less, obscure.

To take just one example, delavirdine has a chemical name 1-(3-((1-Methylethyl)amino)-2-pyridinyl)-4-((5-((methylsulfonyl)amino)-1H-indol-2-yl)carbonyl)piperazine.

Examiner's Conclusion

The Examiner concludes that Claims 1-14 and 17-20 are free of the prior art because the prior art did not teach or suggest administering ddI and Indinavir until viral replication is effectively suppressed, and then administering a gene delivery complex as claimed. Finzi et al. (Science. Nov. 14, 1997, Vol. 278, pg 1295-1300) are said to have

taught administering reverse transcriptase inhibitors and protease inhibitors to HIV patients. However, the Examiner admits that Finzi et al. did not relate to administering DNA encoding the marker protein luciferase to the brain of mice as taught by Boussif et al (PNAS, Aug. 1995, Vol. 92. pg 7292-7301) of record, administering DNA encoding a marker protein to cells in vitro as taught by Zanta et al. (Bioconjugate Chem. 1997. Vol. 8. pg 839-844) of record, administering DNA encoding a marker protein to cells in vitro as taught by Behr et al. (US Patent 6,013,240) of record, or administering virus encoding integrase-defective HIV to cells in vitro as taught by Cara et al. (Virology, 1995, Vol. 208, pg 242-248). The following references have also been reviewed: Lori, Science, 1994, Vol. 266, pg 801-805; Lori, AIDS Res. Hum. Retrovir., 1997. Vol. 13, pg 1403-1409; Lori, AIDS Res. Hum. Retrovir., 1995, Vol. 11, pg 1149-1151; Hollinshead, US Patent 5,747,526;

Malley US Patent 5,521,161 -,

Malley, US Patent 5,736,526-,

Lin, US Patent 5,719,132;

Lori, US Patent 6,046,175

Malley, US Patent 6,093,702;

Lori, US Patent 6,194,390 ;

Critchfield, US Patent 6,274,611;

Lisziewicz, US Patent 6,114,312;

Lisziewicz, US Patent 6,251,874;

Lisziewicz, US Patent 5,977,086.

Response

The applicants thank the Examiner for this candid assessment and thorough search.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982), In re Vogel, 422 F.2d 438,164 USPQ 619 (CCPA 1970); and, In re Thorington, 418 F.2d 528,163 USPQ 644 (CCPA 1969). A timely filed terminal disclaimer in compliance with 37 CFR 1.321 (c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See37CFR1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-14 and 17-20 over USPN 6,420,176

Claims 1-14 and 17-20 have been rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-14 of U.S. Patent No. 6,420,176 in view of the disclosure of 6,420,176. The Examiner points out that the claims of '176 are directed toward a gene delivery complex comprising DNA encoding an immunogenic protein operably linked to a promoter and mannosylated polyethylenimine. The Examiner admits that the claims of '176 do not require administration as required in the instant claims or administration of antiretroviral drug therapy, but adds that MPEP 804 states the specification may be used as a dictionary to learn the meaning of a term in the patent claim. In this case, the Examiner says that one of skill would look to the specification to determine the asserted utility of the product. The disclosure taught administering the gene delivery complex after suppressing viral replication using antiretroviral drug therapy (col. 12, lines 11 -51, see especially lines 2027). Thus, the

Examiner concludes that it would have been obvious to one of ordinary skill in the art at the time the invention was made to administer the gene delivery complex in combination with drug therapy as claimed.

Response

The applicants respectfully request this issue be deferred until agreement on the Claims has been reached.

Claims 1-14 and 17-20 over USPN 6,130,089

Claims 1-14 and 17-20 have been rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-8 of U.S. Patent No. 6,130,089 in view of the disclosure of 6,130,089. The Examiner states that the '089 claims a method of administering a gene delivery complex but does not claim the method requires administering an antiretroviral drug therapy. However, the Examiner points out that the disclosure of '089 taught using the method after administering an antiretroviral drug therapy and suppressing retroviral replication (col. 7, lines 5-33).

Response

The Applicants respectfully submit that this objection is not applicable to the amended Claims, because the cited reference, which relates to increasing the concentration of dNTP in the cytosol of cells. The patent does not disclose or discuss the present invention, or the advantages to be obtained thereby.

Claims 1-14 and 17-20 over copending App. No. 10/081922

Claims 1-14 and 17-20 have been provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over the claims of copending Application No. 10/081922. Although the Examiner admits that the conflicting claims are not identical, he takes the position that they are not patentably distinct from each other because they overlap in scope.This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Response

The cited application is a division of USPN 6,420,176, cited above. Accordingly, the applicants respectfully request this issue be deferred until agreement on the Claims has been reached.

Conclusion

For all the above amendments and reasons is respectfully submitted that the Claims are in condition for allowance. Favorable consideration is solicited.

Respectfully Submitted,

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